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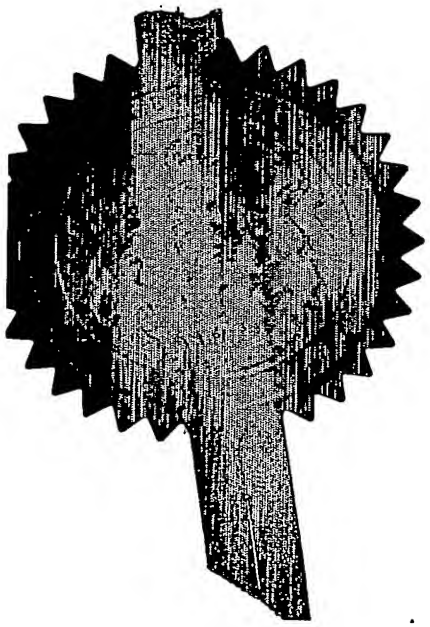

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ull name, address and postcode of the or of ch applicant (underline all surnames)	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire EN11 9BU United Kingdom
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ame of your agent (if you have one)	Dr. W. G. Cole
ddress for service" in the United Kingdom which all correspondence should be sent cluding the postcode)	Merck & Co., Inc. European Patent Department Terlings Park Eastwick Road Harlow Essex CM20 2QR
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I/We request the grant of a patent on the basis of this application.

Signature Dr. W. G. Cole Date 16 May 2003

Name and daytime telephone number of person to contact in the United Kingdom: Dr. W. G. Cole 01279 440163

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THERAPEUTIC AGENTS, COMPOSITIONS, PREPARATIONS AND USES

The present invention relates to a class of sulphonyl derivatives which act on serotonin receptors (also known as 5-hydroxytryptamine or 5-HT receptors). More particularly, the invention concerns phenylsulphonyl derivatives wherein the sulphonyl moiety is also attached to an *N*-phenylethyl-4-fluoro-substituted piperidine. These compounds are potent and selective antagonists of the human 5-HT_{2A} receptor and are therefore useful as pharmaceutical agents, especially in the treatment and/or prevention of adverse conditions of the central nervous system, including sleep disorders such as insomnia and psychotic disorders such as schizophrenia and psychiatric disorders such as anxiety.

Compounds of the invention may display more effective binding to the human 5-HT_{2A} receptor than to other human receptors such as D_2, $5HT_{2C}$ and IKr receptors. They can therefore be expected to manifest fewer side-effects than compounds which do not discriminate in their binding affinity between such receptors. In addition these compounds have lower effects on the IKr receptors and there is a separation of the desired effect from side effects such as cardiac effects.

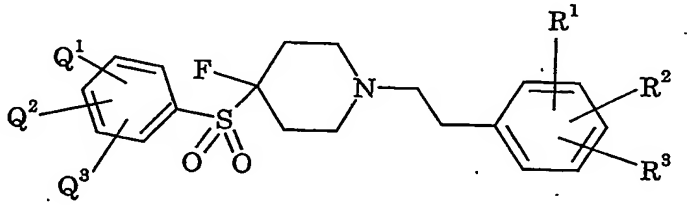
By virtue of their potent human 5-HT_{2A} receptor antagonist activity, the compounds of the present invention are also effective in the treatment of neurological conditions including sleep disorders such as insomnia and also depression, anxiety, panic disorder, obsessive-compulsive disorder, pain, eating disorders such as anorexia nervosa, and dependency or acute toxicity associated with narcotic agents such as LSD or MDMA; and moreover are beneficial in controlling the extrapyramidal symptoms associated with the administration of neuroleptic agents. They may further be effective in the lowering of intraocular pressure.

Various classes of compounds containing *inter alia* a sulphonyl moiety are described in WO 00/43362 WO 96/35666, EP-A-0261688, EP-

0304888, and US Patents 4,218,455 and 4,128,552, DE-A-3901735 and Fletcher *et al, J. Med. Chem.*, 2002, 45, 492-503. None of these publications, however, discloses or suggests the particular class of sulphonyl derivatives provided by the present invention.

The compounds according to the present invention are potent and selective 5-HT_{2A} receptor antagonists having a human 5-HT_{2A} receptor binding affinity (K_i) of 100 nM or less, typically of 50 nM or less and preferably of 10 nM or less. The compounds of the invention may possess at least a 10-fold selective affinity, suitably at least a 20-fold selective affinity and preferably at least a 50-fold selective affinity, for the human 5-HT_{2A} receptor relative to the human dopamine D_2 receptor. The compounds of this invention may possess at least a 10-fold selective affinity, suitably at least a 20-fold selective affinity and preferably at least a 50-fold selective affinity of the human 5-HT_{2A} receptor relative to the IKr. Preferred compounds show selectivities of at least 100 fold.

The present invention provides a compound of formula I, or a salt thereof:



(I)

or a pharmaceutically acceptable salt thereof wherein:

R^1 is hydrogen, fluorine, chlorine or bromine; C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{1-6} alkoxyl; C_{2-6} alkenyloxy; C_{2-6} alkynyloxy; C_{1-6} alkyl substituted by up to 5-fluorine atoms;

R^2 is a hydrogen, fluorine or chlorine atom or a C_{1-4} alkyl, C_{2-4} alkoxy, C_{1-4} alkyl substituted by up to 5 fluorine atoms, C_{1-4} alkoxy substituted by up to 5 fluorine atoms;

R^3 is a hydrogen, fluorine or chlorine atom or a methyl, methoxy, trifluoromethyl, difluoromethyl, trifluoromethoxy or difluoromethoxy group;

Q^1 is hydrogen, fluorine; chlorine; or bromine; C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{1-6} alkoxyl; C_{2-6} alkenyloxy; C_{2-6} alkynyloxy; C_{1-6} alkyl substituted by up to 5-fluorine atoms; nitrile; COQ^4 or CO_2Q^4 where Q^4 is hydrogen or C_{1-6} alkyl; NQ^5Q^6, $CONQ^5Q^6$ or $SO_2NQ^5Q^6$ where Q^5 is hydrogen or C_{1-6} alkyl and Q^6 is hydrogen or C_{1-6} alkyl or Q^5 and Q^6 are joined to form either a 4-7 membered alicyclic ring which may also contain one oxygen or one further nitrogen ring atom or alternatively a heteroaromatic ring of 5-ring atoms 1, 2, 3 or 4 of which may be heteroatoms of which 1, 2, 3 or 4 are nitrogen atoms or 1 or 2 of which are nitrogen atoms and 1 of which is an oxygen or sulphur atom, which heterocyclic ring may optionally be substituted by methyl, ethyl or hydroxyl; hydroxyl; nitro; SOQ^7 or SO_2Q7 where Q^7 is C_{1-4} alkyl; NQ^8COQ^9, $NQ^8CO_2Q^9$ or $NQ^8SO_2Q^9$ where Q^8 is hydrogen or C_{1-4}alkyl, Q^9 is hydrogen or C_{1-4}alkyl or is joined to Q^8 to form a 5-7 membered ring; a carbon-linked heteroaromatic ring of 5 ring atoms 1, 2, 3 or 4 of which may be nitrogen atoms or 1 or 2 of which are nitrogen atoms and 1 of which is an oxygen or sulfur atom or 1 of which is an oxygen or sulfur atom, which heterocyclic ring may optionally be substituted by methyl, ethyl or hydroxyl; a heteroaromatic ring of 6-ring atoms containing 1 or 2 nitrogen ring atoms or a phenyl group either of which is optionally substituted by 1 or 2 fluorine or chlorine atoms or C_{1-4}alkyl, C_{1-4}alkoxy or trifluoromethyl groups;

Q^2 is hydrogen, fluorine or chlorine; a C_{1-4} alkyl; C_{2-4} alkoxy; C_{1-4} alkyl substituted by up to 5 fluorine atoms; C_{1-4} alkoxy substituted by up to 5 fluorine atoms; nitrile or hydroxy;

Q^3 is hydrogen, fluorine or chlorine; a methyl, methoxy, trifluoromethyl, difluoromethyl, trifluoromethoxy or difluoromethoxy;

or Q^2 and Q^3 are joined to form the residue of a 5, 6 or 7 membered carbocyclic ring;

Suitable C_{1-6} alkyl groups can be straight, branched cyclic or combinations thereof. Hence such groups include methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, secbutyl, cyclobutyl, methylcyclopropyl, cyclopentyl, cyclohexyl and straight and branched pentyl and hexyl groups.

Favoured C_{1-6} alkyl groups include methyl, ethyl, n-propyl, cyclopropyl, methylcyclopropyl and the like.

A preferred C_{1-6} alkyl group is the methyl group.

Suitable and favoured alkenyl and alkynyl groups are analogous to the suitable and favoured alkyl groups (excluding C_3 and C_4 rings).

A favoured value for R^3 is hydrogen. A favoured value for R^2 is hydrogen or fluorine. A favoured value for R^1 is hydrogen or fluorine.

Favourably Q^1 is a nitrile group or a carboxamide group or a fluorine atom or a morpholino group or 1,2,3-triazol group.

Favourably Q^1 is para to the sulphonyl group.

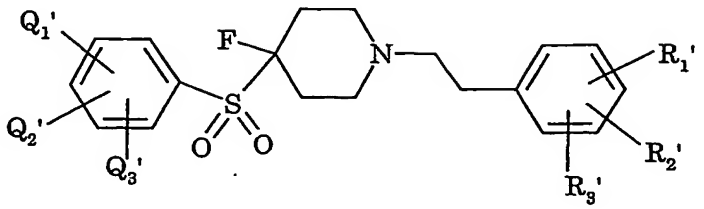
Certain preferred values for the aryl substituent on the sulphonyl group include phenyl, fluorophenyl, difluorophenyl, trifluorophenyl, chlorophenyl, cyanophenyl, methylphenyl, methoxyphenyl, trifluoromethylphenyl, fluorochlorophenyl, fluorocyanophenyl, difluorocyanophenyl, methylfluorophenyl, methoxyfluorophenyl and fluorotrifluoromethylphenyl, amidophenyl, morpholinophenyl, and 1, 2, 3-triazolylphenyl.

Apt values for R^1 include hydrogen, fluorine, chlorine, bromine, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, difluoromethyl, pentafluoromethyl, trifluoromethoxy and difluoromethoxy.

Apt values for R^2 include hydrogen, fluorine, chlorine, methyl, methoxy and trifluoromethyl.

Apt values for R^3 include hydrogen and fluorine.

Certain favoured compounds of the invention include those of formula (II):



(II)

and pharmaceutically acceptable salts thereof wherein:

R_1' is hydrogen, fluorine, chlorine, methyl, trifluoromethyl, methoxy or nitrile;

R_2' is hydrogen, fluorine or chlorine;

R_3' is hydrogen or fluorine;

Q_1' is hydrogen, fluorine, chlorine, bromine, methyl, trifluoromethyl, methoxy, carboxamide, nitrile, or 1,2,3-triazolyl;

Q_2' is hydrogen, fluorine or chlorine;

Q_3' is hydrogen or fluorine.

In certain preferred compounds of formula (II) R_1' is hydrogen or fluorine, R_2' is hydrogen or fluorine and R_3' is hydrogen.

In certain preferred compounds of formula (II) Q_1' is at the 4-position and is hydrogen, fluorine, carboxamide, nitrile or 1,2,3-triazolyl, Q_2' is hydrogen or fluorine and Q_3' is hydrogen.

In certain particularly preferred compounds of this invention the terminal substituent on the alkylene chain is a 2,4-difluorophenyl group.

In certain particularly preferred compounds of this invention the terminal substituent on the sulfonyl group is a 4-benzonitrile or 4-fluorophenyl groups. The 4-(1,2,3-triazolyl)phenyl group is also particularly apt.

Specific compounds of this invention include those compounds exemplified hereinafter and their pharmaceutically acceptable salts.

The compounds of formula (I) form salts, for example pharmaceutically acceptable salts. Suitable salts include salts with pharmaceutically acceptable acids such as hydrochloric, sulphuric, phosphoric acetic, benzoic, methanesulfonic, lactic, citric and like acids. When the compounds of formula I contain an acidic function they can be zwitterionic or may form a salt with a pharmaceutically acceptable anion such as sodium, potassium, calcium, magnesium ion or an organic amine the nitrogen or which is more than that of the piperidine nitrogen in the compound of formula (I).

The invention also provides pharmaceutical compositions comprising a compound of formula I or pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier. One or more such compounds may be present but generally one is preferred. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the compositions may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. An erodible polymer containing the active ingredient may be envisaged. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is

meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Favoured unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

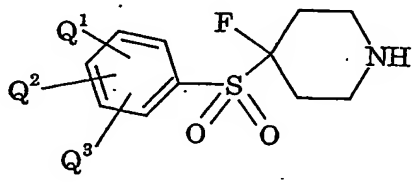
The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment envisaged herein, for exmaple of insomnia or schizophrenia, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to

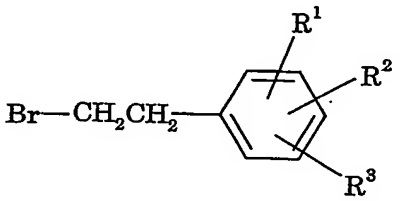
4 times per day but preferably once per day, for example before going to bed.

If desired, the compounds according to this invention may be co-administered with another sleep inducing or anti-schizophrenic or anxiolytic medicament. Such co-administration may be desirable where a patient is already established on sleep inducing or anti-schizophrenic or anxiolytic treatment regime involving other conventional medicaments.

The compounds of the formula (I) may be prepared by the reaction of the compounds of the formulae (III) and (IV)



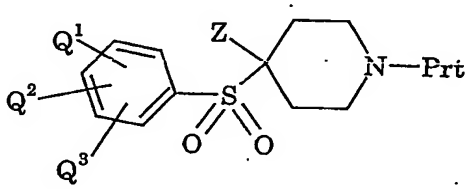
(III)



(IV)

under conventional reaction conditions for alkylation. Such conditions include the use of a suitable solvent such as tetrahydrofuran or acetonitrile at a conventional temperature such as 80°C to 90°C. A catalytic quantity of NaI, K_2CO_3, AgO or the like may be employed in the conventional manner.

If desired the compound of formula (III) may be generated beforehand or in situ by removal of a protecting group from a compound of the formula (Va)

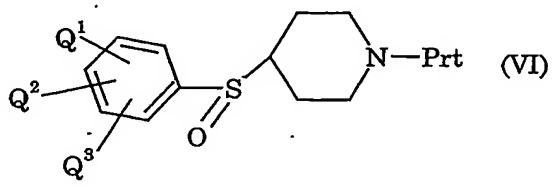


(Va) Z = F
(Vb) Z = H

wherein Prt is a protecting group, for example a benzyloxycarbonyl group which can be removed by treatment with trifluoroacetic acid or HCl/ethanol.

The compound of formula (Va) can be prepared from the corresponding compound of the formula (Vb) by reaction with a strong base such as nBuLi and a fluorinating agent such as $(PhSO_2)_2NF$. This reaction will normally take place in a solvent such as tetrahydrofuran at a temperature of -78°C to 25°C.

In an alternative process the compounds of the formula (Va) may be prepared by the reaction of the compound of the formula (VI):



(VI)

initially with a fluorinating agent such as diethylaminosulfur trifluoride for example in the presence of antimony trifluoride in an inert solvent such as dichloromethane (for example at ambient temperature) and then treating the resulting compound with an oxidizing agent such as metachloroperbenzoic acid (for example in an inert solvent such as dichloromethane at ambient temperature).

The compound of the formula (VI) can be prepared by oxidizing the corresponding thioether with a mild oxidizing agent such as oxone on wet alumina in a solvent such as chloroform at ambient temperature. The thioether may be prepared by the reaction of a thiol A-SH with a protected (for example with a BOC group) 4-methanesulfonyloxy piperidine under conventional conditions such as in acetronitrile at room temperature in the presence of K_2CO_3.

The compounds of the formula (I) may also be prepared by the fluorination of the corresponding compound which possesses a hydrogen

atom instead of the fluorine atom of the compound of formula (I). This may be effected using a fluorinating agent such as $(PhSO_2)_2NF$ and a strong base such as NaHMDS at -78°C to 25°C in an inert solvent such as tetrahydrofuran.

In cases where any of the substituents in any of the compounds require protection during any of the preceeding reactions this may be effected in conventional manner. Alternatively there may be instances where a particular substituent may be introduced after the above reactions are performed. Thus for example where a nitrile is required as a substituent it may be introduced by replacing a bromine atom, for example reacting the appropriate bromo-compound of the formula (I) in an anhydrous solvent such as dimethylformamide with zinc cyanide in the presence of tetrakis(triphenylphosphine)palladium with heating, for example to 85-95°C. Introduction of a nitrile or heterocycle can be also performed by replacement of fluorine by nucleophilic displacement, for example by heating with NaCN or a triazole in DMSO. Other modifications of substituents can be carried out by conventional art methods, for example as set out in WO 00/43362 or Fletcher *et al, J. Med. Chem.*, 2002, 45, 492-503.

Compounds were tested at the 5-HT_{2A} receptor as well as IKr using the methodology described in Fletcher *et al, J. Med. Chem.*, 2002, 45, 492-503.

EXAMPLE 1

4-(4-Bromophenylsulfonyl)-1-[2-(2,4-Difluorophenyl)ethyl]-4-fluoropiperidine

To a suspension of wet alumina (10% water, 13 g) in chloroform (60 mL), was added, N-BOC 4-(4-bromophenylthio)piperidine (prepared according to Fletcher, S. R. *et. al. J. Med. Chem.* 2002, 45, 492-503), followed by oxone (24 g). The reaction was stirred for 3 h, filtered and chromatographed on silica eluting with 50% EtOAc/isohexane to obtain N-BOC 4-(4-bromophenylsulfinyl)piperidine (3.5 g, 69%): δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s), 1.55-1.8 (4H, m), 2.6-2.75 (3H, m), 4.25 (2H, m), 7.47 (2H, d), 7.67 (2H, d).

N-BOC 4-(4-bromophenylsulfinyl)piperidine (3.17 g, 8.5 mmol) was dissolved in dichloromethane (50 mL) and antimony trichloride (194 mg, 0.85 mmol) was added, followed by diethylaminosulfur trifuoride (2.8 mL, 0.022 mol). The reaction mixture was stirred for 16 h at room temperature, quenched with cold, saturated sodium bicarbonate solution and the product extracted into ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was dissolved in dichloromethane (50mL) and combined with a dichloromethane solution of *m*CPBA (7.3 g, 0.021 mol of 50-55% *m*CPBA in 30 mL dichloromethane was dried over $MgSO_4$, filtered and added to the reaction). The reaction mixture was stirred at 25°C for 2 h, then quenched with saturated sodium metabisulfite. The product was extracted into dichloromethane, and the organic layer washed with saturated sodium bicarbonate solution and brine. After drying over $MgSO_4$, the solvent was removed *in vacuo* and the residue chromatographed on silica, eluting with 10% EtOAc/isohexane to obtain N-BOC 4-(4-bromophenylsulfonyl)-4-fluoropiperidine as a white solid (2.3 g, 70%): δ_H (360 MHz, $CDCl_3$) 1.46 (9H,s) 1.9 (2H, m), 2.02-2.3 (2H, m), 2.9 (2H, m), 4.2 (2H, m), 7.8 (4H, dd).

N-BOC 4-(4-Bromophenylsulfonyl)-4-fluoropiperidine (2.3 g, 5.5 mmol) was dissolved in 6 N HCl (30 mL) and ethanol was added until the cloudy solution became clear (ca. 20 mL). The reaction mixture heated to 85°C and stirred at that temperature for 16 h. The reaction mixture was cooled, the ethanol evaporated and the acidic solution made basic by the addition of 5 N NaOH. The product was extracted into EtOAc and the organic layer washed with brine and dried over $MgSO_4$. 4-(4-Bromophenylsulfonyl)-4-fluoropiperidine hydrogen chloride was obtained as a white solid after evaporation of the solvent *in vacuo* (1.4 g, 80%): δ_H (360 MHz, $CDCl_3$) 1.84 (2H, dt), 2.04-2.22 (2H, m), 2.82 (2H, dt), 3.09 (2H, dt), 7.75 (4H, m). *m/z* (ES^+) 322, 324 (M+1).

4-(4-Bromophenylsulfonyl)-4-fluoropiperidine hydrogen chloride (1.4 g, 4mmol) was dissolved in acetonitrile and potassium carbonate (1.4 g, 0.01mol) was added, followed by 2,4-difluorophenethyl bromide (prepared as described in WO0053362, July 27 2000; 1.3 g, 6 mmol). The reaction was heated to reflux for 16 h. After cooling, the reaction mixture was partitioned between EtOAc and water and the organic layer washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica eluting with 30% EtOAc/isohexane to obtain the title compound as a white solid (0.950 g, 51%): δ_H (360 MHz, $CDCl_3$) 1.86 (2H, t), 2.22-2.39 (4H, m), 2.57 (2H, t), 2.76 (2H, t), 2.93 (2H, m), 6.76 (2H, m), 7.13 (1H, m), 7.74 (4H, m). *m/z* (ES^+) 462, 464 (M+1).

EXAMPLE 2

1-[2-(2,4-Difluorophenyl)ethyl]-4-fluoro-4-(4-fluorophenylsulfonyl)piperidine

Method 1

Sodium hexamethyldisilylazide (1.0 M in THF; 0.3 mL, 0.3 mmol) was added dropwise to a stirred solution of 1-[2-(2,4-difluorophenyl)ethyl]-4-(4-fluorophenylsulfonyl)piperidine (95.8 mg, 0.25 mmol) (prepared

according to Fletcher, S. R. *et. al. J. Med. Chem.* 2002, 45, 492-503) in THF (0.5 mL) at –78°C. The solution was warmed to 0°C, stirred for 5 min, then re-cooled to –78°C. A solution of N-fluorobis(phenylsulfonyl)amine (80.8 mg, 0.38 mmol) in THF (0.25 mL) was added and the mixture was allowed to reach ambient temperature, then stirred for 15 min. The reaction was quenched by addition of saturated aqueous NH_4Cl (1 mL), then partitioned between water (20 mL) and EtOAc (20 mL). The organic fraction was dried over Na_2SO_2, filtered and concentrated *in vacuo* and the crude material purified by column chromatography (silica, 30% EtOAc/isohexane) to afford the title compound as a white solid (19 mg): δ_H (500 MHz, DMSO) 1.79-1.83 (2H, m), 2.20-2.19 (4H, m), 2.52-2.55 (2H, m), 2.73-2.76 (2H, m), 2.95-2.97 (2H, m), 7.00-7.04 (1H, m), 7.14-7.19 (1H, m), 7.36-7.41 (1H, m), 7.56-7.61 (2H, m), 7.96-7.99 (2H, m). *m/z* (ES^+) 402 (100%, $[MH]^+$).

Method 2

n-Butyllithium (1.6 M in isohexanes; 13 mL, 20.8 mmol) was added dropwise to a stirred solution of N-BOC 4-(4-fluorophenylsulfonyl)piperidine (6 g, 17.4 mmol) in THF (70 mL) at –78°C. After 1 h, a solution of N-fluorobis(phenylsulfonyl)amine (6.04 g, 19 mmol) in THF (17 mL) was added dropwise and the mixture was brought to ambient temperature, stirred for 1 h, then quenched by the addition of water (1 mL) and partitioned between saturated aqueous NH_4Cl (80 mL) and EtOAc (80 mL). The organic fraction was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica, 20% EtOAc/isohexane) afforded N-BOC 4-fluoro-4-(4-fluorophenylsulfonyl)piperidine as an off-white solid (4.8 g): δ_H (360 MHz, $CDCl_3$) 1.46 (9H, s), 1.80-1.95 (2H, m), 2.05-2.30 (2H, m), 2.90-3.00 (2H, m), 4.12-4.22 (2H, m), 7.28 (2H, t, *J* 8.5 Hz), 7.93-7.96 (2H, m). *m/z* (ES^+) 261 $[(M\text{-}BOC)H]^+$

N-BOC 4-fluoro-4-(4-fluorophenylsulfonyl)piperidine (2 g, 5.5 mmol) was suspended in a mixture of EtOH (50 mL) and 6 N HCl (25 mL) and the mixture heated to 80°C until dissolution occurred. The solution was then concentrated in vacuo and the resulting residue washed with a 10:1 mixture of Et_2O and EtOAc (50 mL) to afford 4-fluoro-4-(4-fluorophenylsulfonyl)piperidine hydrogen chloride as a white solid.

4-Fluoro-4-(4-fluorophenylsulfonyl)piperidine hydrogen chloride was alkylated with difluorophenethyl bromide as described in Example 1 and recrystallised from 50% EtOAc/isohexane to afford the title compound, analytically consistent with the previous data.

EXAMPLE 3

4-{1-[2-(2,4-Difluorophenyl)ethyl]-4-fluoropiperidin-4-yl}sulfonylbenzonitrile

Method 1

4-(4-Bromophenylsulfonyl)-1-[2-(2,4-Difluorophenyl)ethyl]-4-fluoropiperidine (0.350 g, 0.758 mmol) was dissolved in anhydrous DMF (10 mL) and zinc cyanide (0.090 g, 0.758 mmol) added. The solution was degassed with nitrogen for 5 minutes and tetrakis(triphenylphosphine) palladium (100 mg) added. The reaction was heated to 85°C for 2h. Another 100 mg of tetrakis(triphenylphosphine)palladium (0) was added followed by another 100mg after 0.5 h. Another 100 mg of palladium catalyst was then added and the reaction heated at 95°C for 72 h. The reaction mixture was partitioned between EtOAc and water, the organic layer collected and washed with water (x 3) and brine, then dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue chromatographed on silica eluting with 10-25% EtOAc/isohexane to obtain a solid that was recrystallised from EtOAc/isohexane to give the title compound as a white solid (0.153g): δ_H (400MHz, $CDCl_3$) 1.87 (2H,m), 2.33

(4H,m), 2.58 (2H,m), 2.76 (2H,m), 2.94 (2H,m), 6.78 (2H,m), 7.13 (1H,m), 7.88 (2H,d), 8.04 (2H,d).

Method 2

1-[2-(2,4-Difluorophenyl)ethyl]-4-fluoro-4-(4-fluorophenylsulfonyl)piperidine 25 mg, 0.062 mmol), sodium cyanide (20 mg, 0.41 mmol) and DMSO (0.5 mL) were combined and heated to 120°C for 18 h. On cooling, water (5 mL) was added and the resulting precipitate isolated by filtration. The residue was washed with water (10 mL) and dried by a continuous stream of air to afford the title compound (10 mg), analytically consistent with the previous data.

Method 3

N-BOC 4-(4-bromophenylsulfonyl)piperidine (25 g, 62 mmol) (prepared according to Fletcher, S. R. *et. al. J. Med. Chem.* 2002, 45, 492-503), zinc cyanide (8.73 g, 74 mmol) and tetrakis(triphenylphosphine)palladium (0) (3.58 g, 3.1 mmol) were combined in N-methylpyrrolidine (250 mL) and the mixture heated at 160°C for 30 min. On cooling, the reaction mixture was partitioned between EtOAc (250 mL) and saturated aqueous $NaHCO_3$ (200 mL). The organic fraction was washed with water (2 x 150 mL) and brine (150 mL), dried over $MgSO_4$ and concentrated in vacuo to approximately 100 mL, at which point precipitation began to occur. Et_2O (500 mL) was added and the resulting precipitate was filtered off, washed with further Et_2O (200 mL) and dried in a vacuum oven to afford N-BOC 4-(piperidin-4-ylsulfonyl)benzonitrile (9.9 g). δ_H (500 MHz, DMSO) 1.30-1.40 (2H, m), 1.37 (9H, s), 1.80-1.85 (2H, m), 2.65-79 (2H, m), 3.60-3.68 (1H, m), 3.95-4.05 (2H, m), 8.04 (2H, d *J* 8.5 Hz), 8.17 (2H, d *J* 8.5 Hz).

n-Butyllithium (1.6 M in isohexanes; 18.3 mL, 29 mmol) was added to a stirred solution of 2,2,6,6-tetramethylpiperidine (5.4 mL, 32 mmol) in THF (50 mL) at –78°C followed, after 5 min, by a solution of N-BOC 4-

(piperidin-4-ylsulfonyl)benzonitrile (9.9 g, 29.3 mmol) in THF (100 mL). The solution was warmed to –10°C and stirred for 90 min prior to addition of a solution of N-fluorobis(phenylsulfonyl)amine (10.1 g, 32 mmol) in THF (40 mL). The reaction mixture was warmed to ambient temperature, stirred for 30 min, then partitioned between EtOAc (150 mL) and saturated aqueous NH_4Cl (150 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated in vacuo and the crude product purified by column chromatography (silica, 20% EtOAc/isohexane) to afford N-BOC 4-(4-fluoropiperidin-4-ylsulfonyl)benzonitrile (6 g): δ_H (500 MHz, DMSO) 1.41 (9H, s), 1.82-1.90 (2H, m), 1.96-1.11 (2H, m), 2.82-2.93 (2H, m), 3.95-4.05 (2H, m), 8.09 (2H, d *J* 8.2 Hz), 8.22 (2H, d *J* 8.5 Hz).

N-BOC 4-(4-fluoropiperidin-4-ylsulfonyl)benzonitrile was deprotected and alkylated by the methods described in Examples 2 and 1 respectively to afford the title compound, analytically consistent with the previous data.

EXAMPLE 4

4-{1-[2-(2,4-Difluorophenyl)ethyl]-4-fluoropiperidin-4-yl}sulfonylbenzamide

Water (0.5 mL), K_2CO_3 (9 mg, 0.065 mmol) and finally aqueous hydrogen peroxide (*circa* 50%, 0.05 mL, *circa* 0.7 mmol) were added sequentially to a vigorously stirred solution of 4-{1-[2-(2,4-Difluorophenyl)ethyl]-4-fluoropiperidin-4-yl}sulfonylbenzonitrile (53 mg, 0.13 mmol) in DMSO (1 mL). After 30 min, the reaction mixture was partitioned between EtOAc 20 mL) and brine (20 mL) and the organic fraction dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography (silica, 10% EtOH/EtOAc) afforded the title product as a white solid (8 mg): δH (500 MHz, DMSO) 1.75-1.85 (2H, m), 2.02-2.20 (4H, m), 2.50-2.55 (2H, m), 2.70-2.78 (2H, m), 2.91-2.99 (2H, m), 6.98-7.02 (1H, m), 7.11-7.18 (1H, m), 7.31-7.41 (1H, m), 7.81 (1H,

s), 7.97 (2H, d *J* 8.4 Hz), 8.13 (2H, d *J* 8.3 Hz), 8.25 (1H, s). *m/z* (ES^+) 427 $[MH]^+$

EXAMPLE 5

4-{4-Fluoro-1-[2-(2-fluorophenyl)ethyl]piperidin-4-ylsulfonyl}benzamide

A solution of N-BOC 4-(4-fluoropiperidin-4-ylsulfonyl)benzonitrile (1 g, 2.7 mmol) and potassium trimethylsilanolate (346 mg, 2.7 mmol) in toluene (12 mL) was heated to reflux for 2 h. On cooling, the reaction mixture was partitioned between saturated aqueous NH_4Cl (20 mL) and EtOAc (20 mL) and the aqueous portion extracted with further EtOAc (2 x 20 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated and the residue purified by column chromatography (silica, 30-80% EtOAc/isohexane) to afford N-BOC 4-(4-fluoropiperidin-4-ylsulfonyl)benzamide (350 mg): δ_H (500 MHz, DMSO) 1.47 (9H, s), 1.82-1.94 (2H, m), 2.12-2.28 (2H, m), 2.89-2.99 (2H, m), 4.10-4.20 (2H, m), 5.90-6.00 (1H, m), 6.18-6.28 (1H, m), 8.02 (4H, s).

N-BOC 4-(4-fluoropiperidin-4-ylsulfonyl)benzamide was deprotected and alkylated by the methods described in Examples 2 and 1 respectively to afford the title compound as a white solid. δ_H (500 MHz, DMSO) 1.78-1.83 (2H, m), 2.05-2.20 (4H, m), 2.53-2.56 (2H, m), 2.74-2.77 (2H, m), 2.96-2.97 (2H, m), 7.10-7.14 (2H, m), 7.22-7.26 (1H, m), 7.30-7.34 (1H, m), 7.70 (1H, s), 7.97 (2H, d *J* 8.3 Hz), 8.12-8.14 (2H, m), 8.25 (1H, s). *m/z* (ES^+) 409 $[MH]^+$.

EXAMPLE 6

4-(4-{1-[2-(2,4-Difluorophenyl)ethyl]-4-fluoropiperidin-4-ylsulfonyl}phenyl)morpholine

4-(4-Bromophenylsulfonyl)-1-[2-(2,4-Difluorophenyl)ethyl]-4-fluoropiperidine (25 mg, 0.054 mmol) was dissolved in anhydrous toluene (1.5 mL). Morpholine (0.01 mL, 0.108 mmol) and *rac*-2,2'-

m/z (ES^+) 373 $[MH]^+$.

4-{4-Fluoro-1-[2-(4-fluorophenyl)ethyl]piperidin-4-ylsulfonyl}benzamide

m/z (ES^+) 409 $[MH]^+$.

4-[4-Fluoro-1-(2-phenylethyl)piperidin-4-ylsulfonyl]benzamide

m/z (ES^+) 391 $[MH]^+$.

1-[2-(2,4-Difluorophenyl)ethyl]-4-fluoro-4-(phenylsulfonyl)piperidine

m/z (ES^+) 384 $[MH]^+$.

4-Fluoro-1-(2-(2-fluorophenyl)ethyl]-4-(phenylsulfonyl)piperidine

m/z (ES^+) 366 $[MH]^+$.

4-Fluoro-1-(2-(4-fluorophenyl)ethyl]-4-(phenylsulfonyl)piperidine

m/z (ES^+) 366 $[MH]^+$.

4-Fluoro-1-(2-phenylethyl)-4-(phenylsulfonyl)piperidine

m/z (ES^+) 348 $[MH]^+$.

1-[2-(2,4-Difluorophenyl)ethyl]-4-fluoro-4-(4-[1,2,3]triazol-1-ylphenylsulfonyl)piperidine

m/z (ES^+) 451 $[MH]^+$.

1-[2-(2,4-Difluorophenyl)ethyl]-4-fluoro-4-(2-fluorophenylsulfonyl)piperidine

m/z (ES^+) 402 $[MH]^+$.

1-[2-(2,4-Difluorophenyl)ethyl]-4-fluoro-4-(3-fluorophenylsulfonyl)piperidine

m/z (ES^+) 402 $[MH]^+$.

4-(4-Chlorophenylsulfonyl)-1-[2-(2,4-difluorophenyl)ethyl]-4-fluoropiperidine

m/z (ES^+) 419 $[MH]^+$.